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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 10/089,450  
Filing Date: March 29, 2002  
Appellant(s): GORR ET AL.

\_\_\_\_\_  
Raymond Wagenknecht  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 5 October 2010 appealing from the Office action mailed 24 September 2009.

**(1) Real Party in Interest**

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The following is a list of claims that are rejected and pending in the application:

Claims 1-3, 17, 22 and 24.

**(4) Status of Amendments After Final**

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

**(5) Summary of Claimed Subject Matter**

The examiner has no comment on the summary of claimed subject matter contained in the brief.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

#### **(7) Claims Appendix**

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

#### **(8) Evidence Relied Upon**

6,096,546	Raskin et al	08-2000
5,959,177	Hein et al	09-1999

Reutter et al, 1996, Plant Tiss. Cult. Biotechnol. 2:142-147

Menon et al, 1988, J. Plant. Physiol. 132:569-574

#### **(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

A. Claims 1-3, 17 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reutter et al (1996, Plant Tiss. Cult. Biotechnol. 2:142-147) in view of Raskin et al (US Patent 6,096,546, filed January 1998).

The claims are drawn to a method of isolating a heterologous protein from culture medium in which transformed *Physcomitrella patens* protonema were grown.

Reutter et al teach growth of *P. patens* protonema transformed with a nucleic acid encoding a heterologous protein in a bioreactor culture (pg 143, paragraph 2-3) and that these protonema produced large amounts of the heterologous protein grown in bioreactor culture (pg 143, paragraph 3; Fig. 2-3; claim 1). Reutter et al also teach that *P. patens* can be grown on inorganic medium (pg 142, paragraph 4). Reutter et al do not disclose isolation of the protein from the culture medium.

Raskin et al teach isolation of biologically active heterologous protein from the medium in which plants are grown (column 9, lines 21-35; column 10, lines 45-58; column 12, lines 22-67; claims 1-11). The heterologous protein was expressed from a construct containing a signal peptide for secretion (column 6, line 63, to column 7, line 20; Fig. 1 and 4). The heterologous proteins include the enzyme xylanase (example 3).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of producing heterologous protein in *P. patens* protonema as taught by Reutter et al, to use a signal peptide in the transformation construct and isolate the protein from media as described in Raskin et al. One of ordinary skill in the art would have been motivated to do so because of the advantages of being able to isolate the protein from the medium (Raskin et al, column 3, lines 42-67).

**B.** Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Reutter et al in view of Raskin et al as applied to claims 1-3, 17 and 24 above, and further in view of Hein et al (US Patent 5,959,177, filed May 1996).

The claim is drawn to a method of isolating antibody from culture medium in which transformed *Physcomitrella patens* protonema were grown.

The teachings of Reutter et al in view of Raskin et al are discussed above. Reutter et al in view of Raskin et al do not teach expression of antibodies in the plants.

Hein et al teach production of antibody in plants (column 46, line 34, to column 49, line 40).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of isolating heterologous protein from culture medium in which transformed *Physcomitrella patens* protonema were grown as taught by Reutter et al in view of Raskin et al to use an antibody as the heterologous protein as described in Hein et al. One of ordinary skill in the art would have been motivated to do so because of the advantages of a system in which large quantities of an economically important heterologous protein can be produced and isolated. It would have been obvious to one of skill in the art to express a Fab in the plants, because of the suggestion of Hein et al to do so (column 11, lines 53-56).

#### **(10) Response to Argument**

A. The rejection of claims 1-3, 17 and 24 under 35 U.S.C. 103(a) as being unpatentable over Reutter et al (1996, Plant Tiss. Cult. Biotechnol. 2:142-147) in view of Raskin et al (US Patent 6,096,546, filed January 1998).

Applicant urges that Raskin's methods are directed towards exploitation of features found only in higher order plants; Raskin uses only higher order plants, which have vascular systems, roots, vessels and leaf hydathodes (Brief pg 15-16).

This is not persuasive because Raskin exploits endoplasmic reticulum-mediated secretion, a system used in all eukaryotes. Raskin was not interested in developing a new mechanism for plant tissues to produce protein, but merely in finding a cheaper way to isolate proteins plants produce by secretion (see *e.g.*, column 2, lines 29-50). Reutter et al's culture method for protonema means that many of the cost obstacles for plants do not apply to expression of proteins in mosses. Taking that one final step of isolating the heterologous protein from the medium instead of extracting it from the protonema themselves is merely an obvious next step in light of what is known about secretion in eukaryotes, particularly other cell-wall containing organisms like higher plants.

Applicant urges that the claims are drawn to methods that obtain secreted heterologous proteins from the protonema various moss species without disrupting cells; protonema lack true organs, including roots, vessels and leaf hydathodes and thus lack the plant structures relied upon in Raskin (Brief pg 16).

This is not persuasive. The mechanism Raskin relies upon is endoplasmic reticulum-mediated secretion, using a signal peptide for secretion (Raskin, column 6, line 63, to column 7, line 20; Fig. 1 and 4). It is noted that Raskin makes clear that plant cells can secrete

heterologous proteins into media in which they are grown (column 2, lines 1-19), and discusses the use of hairy root cultures to produce antibodies secreted into and isolatable from the medium (column 3, lines 16-23).

Applicant urges that Raskin teaches methods used in higher order plants and Raskin relies on roots and leaf hydathodes and other structures producing an exudate (Brief pg 17-18).

This is not persuasive. Raskin teaches isolation from the medium of protein expressed using a secretion signal sequence.

Applicant urges that Raskin's examples are drawn solely to root and leaf structures of higher order plants (Brief pg 18-20).

This is not persuasive because Raskin teaches that plant portions, which may be parts of a plant tissue, may be used (column 4, lines 23-25) and at no point limits the material used to roots and leaves (see column 4, lines 18-25).

Applicant urges that Raskin can retrieve heterologous proteins from roots and leaf hydathodes by collecting an exudate, which Raskin says oozes out via xylem pressure, diffusion, or secretion; the Reski declaration indicates that rhizosecretion and guttation require structures that are lacking in moss and liverwort protonema, confirming that Raskin is limited to higher order plants (Brief pg 20-22).

This is not persuasive. The mechanism Raskin relies upon is endoplasmic reticulum-mediated secretion, using a signal peptide for secretion (Raskin, column 6, line 63, to column 7, line 20; Fig. 1 and 4). Secretion occurs in moss cells as well as in plants (see Menon et al, 1988, J. Plant. Physiol. 132:569-574, abstract and pg 572, right column, paragraph 1).



Applicant urges that since the examiner did not demonstrate isolation of heterologous proteins from plants grown without disruption or tissues as applied to protonema, the rejection should be reversed (Brief pg 22).

This is not persuasive. This is an obviousness rejection based on a combination of references. That combination makes obvious the claimed invention.

Applicant urges that it is clear from Raskin's teachings that a reasonable expectation of success would require the proposed organism to have roots and leaf hydathodes; as protonema do not have roots, vessels or leaf hydathodes, there would be no reasonable expectation of success and a rejection relying upon an obvious to try analysis is in error (Brief pg 25).

This is not persuasive. It is clear from Raskin's teachings that secretion into the medium of proteins expressed with a secretion signal sequence occurs in plants; while isolation from hydroponic growth requires the structures, isolation from Reutter's culture conditions does not.

Applicant urges that the Reski declaration indicates that since protonema have no roots, vessels or hydathodes, the combination would not have been obvious to try with a reasonable expectation of success (Brief pg 25-26).

This is not persuasive. Reutter et al teach 90% of the claimed invention. They teach growth of *P. patens* protonema transformed with a nucleic acid encoding a heterologous protein in a bioreactor culture (pg 143, paragraph 2-3). They teach that these protonema produced large amounts of the heterologous protein grown in bioreactor culture (pg 143, paragraph 3; Fig. 2-3; claim 1). The only other possible place to isolate the protein from is the medium; one of skill in the art would know, both from knowledge of basic cell biology, and from teachings like Raskin et al, that a secretion signal sequence would be required. It would have been obvious to try

isolation from the medium given the reduction in purification steps and other advantages of being able to isolate the protein from the medium (Raskin et al, column 3, lines 42-67).

Applicant has not shown any unexpected results to overcome this rejection. Applicant has not, for example shown that a showing that use of moss in a bioreactor produced secreted proteins at an unexpectedly high rate compared to use of other cell-wall containing organisms in such a system (plants, fungi, etc).

Applicant urges that diffusion would not permit the crossing of heterologous proteins across the protonema cell wall because the proteins are too large and the cell wall too cross-linked (Brief pg 27-29).

This is not persuasive because endoplasmic reticulum-mediated secretion is the mechanism that applies here.

Applicant urges that facilitated transport would not logically apply to secretion of proteins from protonema because it required ligand specificity and saturation kinetics; given the rigidity of the cell wall, facilitated transport is unthinkable (Brief pg 29-30).

This is not persuasive. First, Raskin specifically defines "facilitated transport" as secretion; see column 4, line 63, quoted on pg 20 of Applicant's brief. It is clear from Raskin's other use of the word secretion, for example at column 2, lines 2-17, that Raskin uses the term to mean secretion through the endoplasmic reticulum, a secretion system used in all eukaryotes. Ligand specificity and saturation kinetics are not involved in endoplasmic reticulum-mediated secretion.

Second, plant cell walls are permeable to proteins as large as 150 kDa, including antibodies, and plants will secrete such proteins fused to signal peptides for secretion (Raskin,

column 2, lines 1-19). Applicant has not indicated why one of skill in the art would think endoplasmic reticulum-mediated secretion would not function in mosses. Applicant, in fact, cannot. It was known in the art that moss cells secrete proteins into medium in which they are grown (see Menon et al, 1988, J. Plant. Physiol. 132:569-574, abstract and pg 572, right column, paragraph 1).

Applicant urges that the approach taken by the instant invention is not facilitated transport or diffusion but secretion using a signal peptide (Brief pg 30).

This is not persuasive because this is the approach taught by Raskin, as discussed above, and in the rejection itself: "The heterologous protein was expressed from a construct containing a signal peptide for secretion (column 6, line 63, to column 7, line 20; Fig. 1 and 4)."

**B.** The rejection of claim 22 under 35 U.S.C. 103(a) as being unpatentable over Reutter et al in view of Raskin et al as applied to claims 1-3, 17 and 24 above, and further in view of Hein et al (US Patent 5,959,177, filed May 1996).

Applicant urges that Reutter et al in view of Raskin et al fail to provide obtaining secreted heterologous proteins from protonema in culture medium without disrupting tissues or cells (Brief pg 31).

This is not persuasive for the reasons detailed above.

Applicant urges that Hein et al teach expression and assembly of foreign multimeric proteins in higher order plants and teach disrupting the plant cells and tissue (Brief pg 31-33).

This is not persuasive because Reutter et al in view of Raskin et al fail to provide obtaining secreted heterologous proteins from protonema in culture medium without disrupting tissues or cells. Hein et al is relied on merely to teach expression of antibodies in plants.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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